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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

In this New Drug Application (NDA) submission, the applicant seeks the approval of Ixazomib (also referred to as Ninlaro®) plus lenalidomide and dexamethasone for the treatment of (b) (4) patients with (b) (4) multiple myeloma ((b) (4) MM). This NDA was based on one pivotal trial, Study C16010, which is a Phase III, randomized, double-blind, multi-center study of Ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone for patients with RRMM. The primary objective of the Study C16010 was to determine whether the addition of Ixazomib to the background therapy of lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with RRMM.

Study C16010 demonstrated superiority in the primary efficacy endpoint, progression-free survival (PFS) per independent review committee (IRC) assessments, for RRMM patients. Based on the 1st interim analysis (IA) of PFS, the estimated hazard ratio (HR) for PFS was 0.74 (95% confidence interval: 0.59 – 0.94, p-value = 0.01) for the Ixazomib arm versus Placebo arm; the median PFS was 20.6 months in Ixazomib arm, and was 14.7 months in placebo arm; the estimated HR for overall survival (OS) was 0.9 (95% confidence interval: 0.62 – 1.32) based on 107 deaths, median OS was not reached for either treatment arm. An updated final analysis of PFS and 2nd interim analysis for other efficacy endpoints were submitted during the review of this NDA submission. Based on this updated analysis, the estimated hazard ratio (HR) for PFS was 0.82 (95% confidence interval: 0.67 – 1.0, p-value = 0.0548) for the Ixazomib arm versus Placebo arm; the median PFS was 20.0 months in Ixazomib arm, and was 15.9 months in placebo arm; the estimated HR for overall survival (OS) was 0.87 (95% confidence interval: 0.64 – 1.18) based on 171 deaths, median OS was not reached for either treatment arm.

The submitted data for 1st interim analysis of PFS per IRC support the applicant's claim of efficacy of Ixazomib in combination with lenalidomide and dexamethasone for patients with (b) (4) multiple myeloma. However, we identified some statistical issues in this submission:

- Although 1st interim analysis results of PFS per IRC crossed the pre-specified superiority boundary, the final analysis results of PFS were not statistically significant.
- There were discordance between PFS per IRC and PFS per investigator. Analysis results for PFS per investigator were not significant for both interim and final analysis.
- There were some discrepancies between 1st interim and final PFS data.

Due to these issues, reliable estimate of the magnitude of treatment effect based on PFS could not be ascertained.

2 INTRODUCTION

2.1 Overview

Ixazomib, a modified peptide boronic acid analog, is Millennium's next-generation proteasome inhibitor after Velcade. According to the Applicant, in contrast to Velcade, Ixazomib demonstrates a faster dissociation rate from the proteasome that may result in enhanced tumor penetration, exhibits antitumor activity in a broader range of tumor xenografts, and has more prolonged tissue penetration. In addition, Ixazomib will be taken orally compared to subcutaneous or intravenous use of Velcade.

The proposed indication submitted in this NDA application is for the treatment of patients with (b) (4) multiple myeloma who have received at least one prior therapy.

Study C16010 is a randomized, double-blinded, multi-center study of Ixazomib plus lenalidomide and dexamethasone versus Placebo plus lenalidomide and dexamethasone in subjects with RRMM. The primary efficacy endpoint is progression-free survival per IRC using International Myeloma Working Group (IMWG) response criteria. The key secondary efficacy endpoints are overall survival (OS) and overall survival in high risk patients harboring Del17.

A total of 722 patients with RRMM were enrolled between 28 August 2012 and 27 May 2014 from 147 study centers in 26 countries. By region, 483 patients (67%) were enrolled from 91 sites in Europe, 143 patients (20%) were enrolled from 35 sites in the Asia-Pacific (APAC) region, and 96 patients (13%) were enrolled from 21 sites in North America (NA). The data cut-off date was 30 October 2014.

The original protocol for Study C16010 was dated 21 February 2012, and the latest version was Amendment 3 dated 08 July 2014.

Throughout this review, patients received Ixazomib plus lenalidomide and dexamethasone or Placebo plus lenalidomide and dexamethasone are referred as "Ixazomib + LenDex" arm or "Placebo + LenDex" arm respectively in the text, the tables/figures.

TABLE 1: LIST OF ALL STUDIES INCLUDED IN ANALYSIS

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects	Enrollment period Geographic region
<i>C16010</i>	Phase 3, randomized, double-blind, multi-center study designed to evaluate the efficacy and safety of Ixazomib plus lenalidomide and dexamethasone versus Placebo plus lenalidomide and dexamethasone in subjects with relapsed/refractory MM	Treatment until progressive disease (PD), death, or any other reason listed in the protocol for mandatory withdrawal.	After treatment discontinuation, subjects were followed for PD every 4 weeks until PD or start of further anti-cancer therapy, after that, patients will be followed every 12 weeks for survival until death or study closure.	N=722	28 August 2012 – 27 May 2014 from 147 study centers in 26 countries

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: [\\CDSESUB1\evsprod\NDA208462\0000](#).

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the pivotal study C16010.

3.1 Data and Analysis Quality

The progression-free survival and censoring status were derived and saved in analysis datasets “ADTTE” for IRC assessment and investigator assessment respectively for both 1st interim and 2nd interim analysis. The statistical reviewer is able to reproduce the derived progression-free survival analysis datasets from the NDA tabulation datasets, except that while comparing 1st interim and final analysis data for PFS per IRC, we found the following data issues which involved 19 patients:

- Observed PFS from 2nd interim analysis was smaller than observed PFS from 1st IA.
- A subject already had an event at 1st IA, but the observed PFS was different between 1st interim and final analysis, and for some cases patients were even censored at final PFS analysis.

The Applicant explained there were 2 major reasons why observed PFS may change between 1st interim and final PFS analyses: First, confirmation of progressive disease (PD) is required by 2 consecutive evaluations (at least 1 week apart); confirmation is not required if PD occurs at the date of the last response assessment before the data cut-off (DCO) date; Second, as Study C16010 is ongoing, PFS assessments could be re-read if new or changed data were received.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The pivotal trial C16010 was a Phase III, randomized, double-blind, multi-center study of Ixazomib versus Placebo for the treatment of patients with RRMM. Approximately 703 patients were planned to be randomized 1:1 to the 2 treatment arms via an interactive voice response system (IVRS). Randomization was stratified by three factors:

- 1 versus 2 or 3 prior therapies;
- Proteasome inhibitor [PI]-exposed versus PI-naïve;
- International Staging System [ISS] stage 1 or 2 versus stage 3

The primary objective of the study was to determine whether the addition of oral Ixazomib to the background therapy of lenalidomide and dexamethasone improved PFS in patients with RRMM. PFS was assessed per IRC using IMWG criteria. Target population was subjects with RRMM who had failed at least one prior line of therapy. Disease status was assessed every 4 weeks until disease progression confirmed by IRC.

In the original protocol, there was one and only analysis for PFS, which was planned at 234 PFS events. With amendment 3 dated 08 July 2014, timing for PFS analysis was revised, one interim efficacy analysis of PFS was added at ~262 PFS events, and the final PFS analysis was changed to when ~365 PFS events occur. Lan-DeMets spending function with O'Brien Fleming boundary was used to determine superiority boundaries for both interim and final PFS analyses.

In the original protocol, the sample size was calculated based on maintaining 80% power to test the first key secondary endpoint OS. There were two interim and one final analyses planned for OS at ~118, ~322, and ~482 deaths respectively. Assuming a hazard ratio of 0.77 (median survival of 30 months in placebo arm versus 39 months in Ixazomib arm), a total of approximately 703 patients would be needed to test OS with 80% power and 2-sided type I error rate of 5%, assuming an average enrollment rate of approximately 13 patients/month for the first 6 months, 30 patients/month thereafter, and approximately 10% dropout rate. With 234 PFS events, it will have 90% power to detect a hazard ratio of 0.66 (median PFS of 11 months for placebo versus 16.8 months for Ixazomib) with a 2-sided alpha level of 0.05.

In the protocol amendment 3, the sample size was the same but the assumption for sample size justification was revised according to the latest research findings. The assumed median PFS was revised to 15 months for the placebo arm and 20.6 months for the Ixazomib arm, the assumed HR was revised to 0.728, and the power for PFS analysis was reduced to 85%. The power analysis for OS in amendment 3 was similar to that in original protocol, except that there would be 3 interim and 1 final analyses of OS at ~154, ~222, ~322, and ~486 deaths respectively.

Reviewer's note:

- The Applicant wrote in the protocol that if PFS achieved superiority at the interim analysis, the final PFS analysis would be non-inferential.
- A final analysis with two-sided significance level of 0.05 after an interim analysis rejecting null hypothesis does not inflate Type I error.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint was progression-free survival, defined as the time from the date of randomization to the date of progression or death due to any cause, whichever occurred first. If no baseline or post-baseline disease assessment available, the PFS time was censored at the date of randomization. Patients without documentation of PD will be censored at the date of last response assessment that is stable disease (SD) or better.

The key secondary efficacy endpoints included:

- Overall survival (OS), which was defined as time from the date of randomization to the date of death due to any cause.
- Overall survival in high risk patients harboring Del17.

3.2.2 Statistical Methodologies

PFS was compared between Ixazomib arm and Placebo arm in the ITT population using the stratified log-rank test. The hazard ratio and corresponding 95% confidence interval (CI) were estimated using the stratified Cox proportional hazard model. Median PFS with 95% CI and survival curves were estimated using Kaplan-Meier method. The primary analysis of PFS was based on IRC assessments using IMWG response criteria.

The Applicant performed three sensitivity analyses of PFS:

- Sensitivity analysis 1: Disease progression documented between scheduled visits was counted as a progression event at the date of disease progression.
- Sensitivity analysis 2: Alternate antineoplastic therapy started prior to disease progression was counted as an event at the date of disease progression
- Sensitivity analysis 3: Death or disease progression after more than 1 missed visit was counted as an event at the date of disease progression

In addition, an analysis of PFS per investigator assessments was performed.

The analyses of overall survival used the same methods as for the analysis of primary endpoint PFS. The significance level (α) for the primary 1st interim analysis of PFS in the NDA application was 0.023 (2-sided) based on 286 PFS events (~78% PFS information). The significance level for the key secondary endpoint OS was <0.0001 based on 107 deaths at the 1st interim analysis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

Intent-to-treat (ITT) population was defined as all randomized subjects. Subjects were analyzed by the treatment arm they were assigned to at randomization. ITT population was the primary analysis population for all efficacy analyses, and was used for descriptions of patient disposition, demographics, and baseline disease characteristics.

The safety population was defined as all randomized subjects who received at least one dose of study treatment.

Study C16010 randomized 722 subjects with RRMM, 360 to Ixazomib arm and 362 to Placebo arm respectively, from 147 study centers in 26 countries. Two patients in the Ixazomib arm, one withdrew consent and the other had serious pretreatment AE, were never dosed with any study treatment and excluded from the safety population. Two placebo regimen patients were erroneously given Ixazomib regimen kits at some cycles during treatment. These 2 patients were excluded from the safety population of the placebo regimen and included in Safety population of the Ixazomib regimen. Thus, the safety population of each treatment regimen included 360 patients.

Subject disposition

At the time of study cutoff of 30 October 2014, 199 (55%) subjects in Ixazomib arm and 188 (52%) subjects in Placebo arm were continuing on treatment, and 161 (45%) subjects in Ixazomib arm and 175 (48%) subjects in placebo arm had discontinued study treatment. The most common reason for discontinuation was progressive disease (23% in Ixazomib arm and 29% in Placebo arm, respectively). The second most common reason for discontinuation was adverse events (13% in Ixazomib arm and 11% in Placebo arm, respectively). Median follow-up time, estimated using reverse Kaplan-Meier method, was 14.8 months for Ixazomib arm and 14.6 months for Placebo arm.

Table 2: Subject disposition, ITT population

	Ixazomib + LenDex	Placebo + LenDex
	(N=360)	(N=362)
	n (%)	n (%)
All randomized	360 (100)	362 (100)
Never Treated	2 (0.6)	0 (0)
Treated	358 (99.4)	362 (100)
Treatment ongoing	199 (55)	187 (52)
Treatment discontinued	161 (45)	175 (48)
Primary reasons for discontinuation of study treatment		
Progressive disease	84 (23)	106 (29)
Adverse event/unacceptable toxicity	46 (13)	40 (11)
Withdrawal by patient	9 (3)	11 (3)
Protocol violation	0 (0)	1 (<1)
Lost to follow-up	2 (<1)	0 (0)
Other	20 (6)	17 (5)
Follow-up time (Months)		
Median	14.8	14.6
Range	(0.1, 23.7)	(0.2, 23.5)

[Source: study C16010 CSR Pages 99 Table 10.b and statistical reviewer's analysis]

Reviewer's note:

- More than 50% of patients in both treatment arms are still on treatment.
- Per the statistical reviewer's analysis, there was one more patient discontinued treatment in the placebo arm than what was presented in Table 10.b in the Study CSR.

Subject demographics and baseline disease characteristics

Subject demographics and stratification factors appeared to be balanced between Ixazomib arm and Placebo arm (Table 3).

TABLE 3: DEMOGRAPHICS AND STRATIFICATION FACTORS, ITT POPULATION

	Ixazomib + LenDex	Placebo + LenDex	Total
	(N=360)	(N=362)	(N=722)
Age (years)			
Mean (SD)	65.5 (9.1)	65.8 (9.7)	65.7 (9.4)
Median	66.0	66.0	66.0
Range	(38.0, 91.0)	(30.0, 89.0)	(30.0, 91.0)
Category, n (%)			
< 65	148 (41.1)	157 (43.4)	305 (42.2)
≥ 65	212 (58.9)	205 (56.6)	417 (57.8)
Sex, n (%)			
Male	207 (57.5)	202 (55.8)	409 (56.7)
Female	153 (42.5)	160 (44.2)	313 (43.3)
Race, n (%)			
White	310 (86.1)	301 (83.2)	611 (84.6)
Asian	30 (8.3)	34 (9.4)	64 (8.9)
Black	7 (1.9)	6 (1.7)	13 (1.8)
Other	6 (1.7)	6 (1.7)	12 (1.7)
Not reported	7 (1.9)	15 (4.1)	22 (3.1)
Line of prior therapy			
1	212 (58.9)	213 (58.8)	425 (58.9)
2 or 3	148 (41.1)	149 (41.2)	297 (41.1)
Proteasome inhibitor			
Exposed	250 (69.4)	253 (70.0)	503 (69.7)
Naïve	110 (30.6)	109 (30.1)	219 (30.3)
ISS Stage at screening			
Stage I or II	314 (87.2)	318 (87.9)	632 (87.5)
Stage III	46 (12.8)	44 (12.2)	90 (12.5)

SD: standard deviation;

[Source: study C16010 CSR Pages 102 Table 10.d and statistical reviewer's analysis]

Baseline disease characteristics are summarized in Table 4. Median time from diagnosis to first dose of study treatment was 42.8 months. Most subjects (74.9%) had IgG or IgA type of myeloma at the study entry. There were 69 (9.6%) high risk patients with deletion in the short arm of chromosome 17p13.1 (del17p).

TABLE 4: BASELINE DISEASE CHARACTERISTICS, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)	Total (N=722)
Time from initial diagnosis to first dose of study treatment (months)			
Mean (SD)	52.6 (37.4)	50.8 (37.7)	51.7 (37.5)
Median	44.2	42.2	42.8
Range	(3.0, 281.1)	(4.2, 306.3)	(3.0, 306.3)
Type of Myeloma at study entry, n (%)			
IgG	207 (57.5)	209 (57.7)	416 (57.6)
IgA	77 (21.4)	53 (14.6)	125 (17.3)
ISS stage at study entry, n (%)			
Stage I	226 (62.8)	233 (64.4)	459 (63.6)
Stage II	89 (24.7)	87 (24.0)	176 (24.4)
Stage III	45 (12.5)	42 (11.6)	87 (12.1)
Baseline ECOG Performance Score, n (%)			
0	180 (50.0)	170 (47.0)	350 (48.5)
1	156 (43.3)	164 (45.3)	320 (44.3)
2	18 (5.0)	24 (6.6)	42 (5.8)
Creatinine clearance (mL/min)			
Mean (SD)	83.0 (30.0)	81.7 (31.6)	82.3 (30.8)
Median	78.4	78.4	78.4
Range	20.3, 232.8	26.6, 233.5	20.3, 233.5
< 60	79 (21.9)	100 (27.6)	179 (24.8)
≥ 60	281 (78.1)	261 (72.1)	542 (75.1)
High risk patients (harboring Del17p)			
Yes	36 (10.0)	33 (9.1)	69 (9.6)
No	324 (90.0)	329 (90.9)	653 (90.4)

SD: standard deviation; ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group;

[Source: Study C16010 CSR Page 109-110 Table 10 f and statistical reviewer's analysis]

Reviewer's note: In table 4, types of myeloma at the study entry per statistical reviewer's analysis were slightly different from what were presented in Table 10.f in the study CSR.

All subjects received at least one prior anti-cancer therapy for MM, and 281 (38.9%) patients received 2 or 3 prior MM therapies.

TABLE 5: PRIOR THERAPIES, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)	Total (N=722)
Line of prior therapies			
1	224 (62.2)	217 (59.9)	441 (61.1)
2	97 (26.9)	111 (30.7)	208 (28.8)
3	39 (10.8)	34 (9.4)	73 (10.1)
Patient categories, n (%)			
Relapsed	276 (76.9)	280 (77.4)	556 (77.1)
Refractory	42 (11.7)	40 (11.1)	82 (11.4)
Refractory and relapsed	41 (11.4)	42 (11.6)	83 (11.5)
Stem cell transplant, n (%)	212 (58.9)	199 (55.0)	411 (56.9)
Autologous	202 (56.1)	193 (53.3)	395 (54.7)
Allogeneic	6 (1.7)	4 (1.1)	10 (1.4)
Both	4 (1.1)	2 (0.6)	6 (0.8)
Prior proteasome inhibitor exposed, n (%)	249 (69.2)	253 (69.9)	502 (69.5)
Refractory to any prior PI therapy	22 (6.1)	17 (4.7)	39 (5.4)
Velcade	248 (99.6)	249 (98.4)	497 (99.0)
Carfilzomib	1 (0.4)	3 (1.2)	4 (0.8)
Velcade and carfilzomib	0	1 (0.4)	1 (0.2)
Prior IMiD therapy exposed	193 (53.6)	204 (56.4)	397 (55.0)
Refractory to any prior IMiD therapy	41 (11.4)	50 (13.8)	91 (12.6)
Lenalidomide	36 (18.7)	34 (16.7)	70 (17.6)
Thalidomide	149 (77.2)	160 (98.4)	309 (77.8)
Lenalidomide and Thalidomide	8 (4.2)	10 (4.9)	18 (4.5)
Corticosteroid contained prior therapy	356 (98.9)	355 (98.1)	711 (98.5)
Dexamethasone	239 (66.4)	238 (65.8)	477 (66.1)
Prednisone	54 (15.0)	57 (15.8)	111 (15.4)
Dexamethasone and prednisone	63 (17.5)	60 (16.6)	123 (17.0)

[Source: Study C16010 CSR Page 105 Table 10.e and statistical reviewer's analysis]

Protocol deviation

Major protocol deviations were defined as: investigation product compliance $\leq 70\%$, inclusion/exclusion issues, excluded concomitant medication taken, major overdose error, and no pregnancy test. A total of 36 subjects (5.0%) (19 [5.3%] in Ixazomib arm and 17 [4.7%] in Placebo arm) had major protocol deviations.

TABLE 6: SUBJECTS WITH IMPORTANT PROTOCOL VIOLATIONS, ITT POPULATION

	Ixazomib + LenDex (N=360) n (%)	Placebo + LenDex (N=362) n (%)
Patients with at least 1 major violation	19 (5.3)	17 (4.7)
Investigational product compliance $\leq 70\%$	7 (2)	8 (2)
Inclusion/exclusion issues	7 (2)	7 (2)
Excluded concomitant medication taken	4 (1)	1 (<1)
Major overdose error	1 (<1)	0
No pregnancy test	0	1 (<1)

[Source: Study C16010 CSR Page 100 Table 10.c and statistical reviewer's analysis]

Reviewer's note: There were 4 more patients (1 more in Ixazomib arm and 3 more in placebo arm) had major violation based on the statistical reviewer's analysis compared to the Table 10.c in the study CSR.

3.2.4 Results and Conclusions

3.2.4.1 Primary Analysis Results of PFS

The primary analysis, which was planned 1st interim analysis of PFS per IRC, was based on 286 progression or death events (~ 78% of planned 365 events) observed at the data cutoff date. The superiority boundary for this primary analysis was 0.023 (two-sided). The primary analysis results are summarized in Table 7 and Figure 1. The observed difference in PFS per IRC between two treatment arms was statistically significant (p-value =0.013). The hazard ratio for Ixazomib versus Placebo was 0.74 (95% CI: [0.59, 0.94]) with estimated median PFS of 20.6 months for Ixazomib arm and 14.7 months for the placebo arm.

TABLE 7: PRIMARY ANALYSIS RESULTS OF PFS PER IRC, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Events (%)	129 (35.8)	157 (43.4)
Progressed	114 (31.7)	145 (40.1)
Died	15 (4.2)	12 (3.3)
Median PFS (months) (95% CI)	20.6 (17.0, NE)	14.7 (12.9, 17.6)
Stratified Hazard Ratio (95% CI)	0.74 (0.59, 0.94)	
P value	0.013	

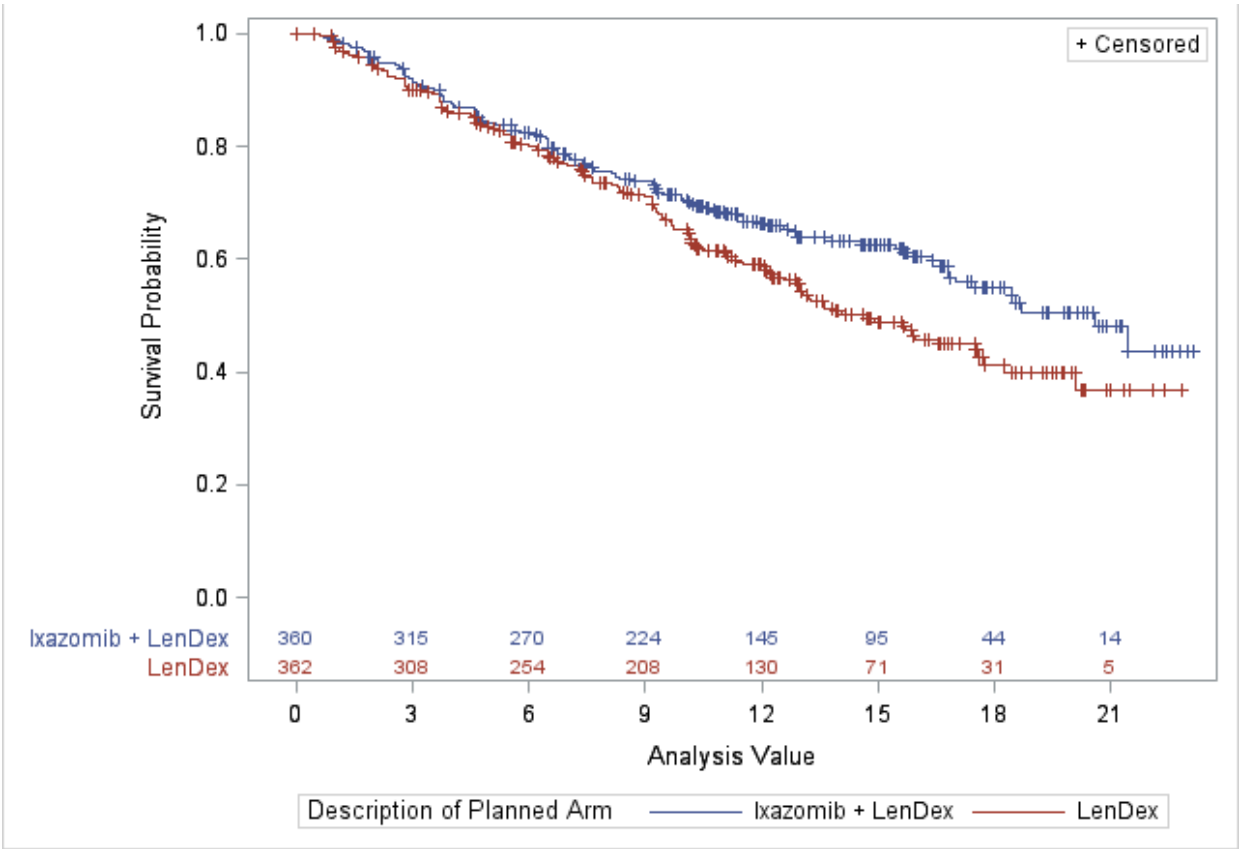
- PFS: progression-free survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Statistical reviewer's analysis]

Figure 1: Kaplan-Meier curve for 1st interim analysis of PFS per IRC, ITT population



[Source: Statistical reviewer's analysis.]

Reviewer's note: In general, results based on interim analysis of PFS are considered robust when they are overwhelmingly significant with a very small p value, for example in the case of lenalidomide plus dexamethasone versus placebo plus dexamethasone for the treatment of previously treated multiple myeloma patients. Please refer to lenalidomide labeling for further details: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021880s041lbl.pdf.

3.2.4.2 Final Analysis Results of PFS

The final analysis of PFS and 2nd interim analysis of other efficacy endpoints was planned when ~365 PFS occurs. The cutoff for this 2nd interim analysis was 12 July 2015. The Applicant submitted the topline results and corresponding data sets on 09 October 2015.

TABLE 8: FINAL ANALYSIS RESULTS OF PFS PER IRC, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Events (%)	177 (47.6)	195 (52.4)
Progressed	158 (42.5)	180 (48.4)
Died	19 (5.1)	15 (4.0)
Median PFS (months) (95% CI)	20.0 (18.0, 23.4)	15.9 (13.2, 18.8)
Stratified Hazard Ratio (95% CI)	0.82 (0.67, 1.0)	
P value	0.0548	

- PFS: progression-free survival; CI: confidence interval; NE: not evaluable/achieved;

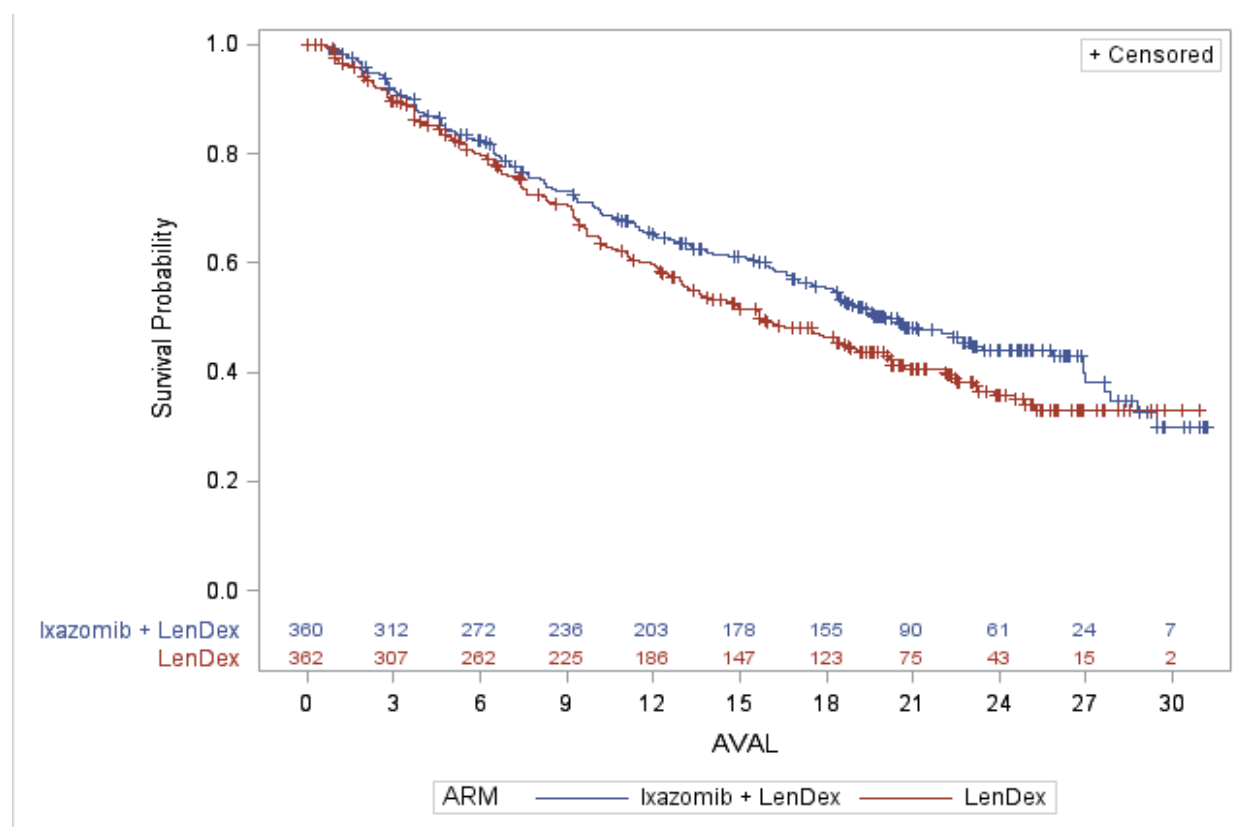
- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Table 1.c in the applicant's RFI response dated October 9, 2015 and Statistical reviewer's analysis]

Reviewer's note: Table 8 and Figure 2 demonstrated that the updated PFS per IRC analysis results were not statistically significant with a p value of 0.0548. The difference in median PFS per IRC observed in this final PFS analysis was reduced to 4.1 months compared to 5.9 months observed in the 1st interim analysis, the estimated HR was 0.82 (95% CI: [0.67, 1.0]).

Figure 2: Kaplan-Meier curve for final analysis of PFS per IRC, ITT population



[Source: Statistical reviewer's analysis.]

3.2.4.3 Discordance between PFS per IRC and Investigator

For both the 1st interim and final PFS data, in addition to analysis of PFS per IRC, an analysis of PFS per investigator was performed as well.

TABLE 9: FIRST INTERIM ANALYSIS RESULTS OF PFS PER INVESTIGATOR, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Events (%)	132 (36.7)	150 (41.4)
Progressed	116 (32.2)	135 (37.3)
Died	16 (4.4)	15 (4.1)
Median PFS (months) (95% CI)	19.6 (17.2, NE)	16.2 (13.9, 19.0)
Stratified Hazard Ratio (95% CI)	0.83 (0.65, 1.05)	
Nominal P value	0.11	

- PFS: progression-free survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Statistical reviewer's analysis]

Reviewer's note: For the 1st IA of PFS per investigators, the observed difference in median PFS between Ixazomib arm and placebo arm was 3.2 months compared to 5.9 months for PFS per IRC, the HR was 0.83 (95% CI: [0.65, 1.05]) , and the nominal p value was 0.11 (Table 9).

Among the 235 patients with PD as assessed by both the IRC and the investigator, the majority (160; 68%) of cases had the same PD date and the PD date differed between the IRC and investigator in 75 cases. To further investigate the differences in the PD dates, the Applicant independently reviewed the investigator-determined dates of progression that were 28 days or more different than those reported by the IRC, which involved 57 out of 75 cases. Applicant's exploration of discrepancy between PFS per IRC and PFS per investigator was listed in Table 10.

TABLE 10: EXPLORATION OF DISCORDANCE BETWEEN IRC AND INVESTIGATOR PD DATES

Dates of PD Used in Additional PFS Sensitivity Analysis for FDA	
PD Cases (n=235)	PD date used in PFS sensitivity analysis reported here
160 cases: not reviewed by Millennium, as PD dates assessed by IRC and investigator agreed	IRC-assessed date
75 cases: IRC and investigator dates did not agree	
18 cases: not reviewed by Millennium, as PD dates assessed by IRC and investigator were within 28 days (1 cycle)	IRC-assessed date
57 cases: reviewed by Millennium, as PD dates assessed by IRC and investigator differed by 28 days or more	
51 cases: Millennium agreed with IRC	IRC-assessed date
3 cases: Millennium agreed with investigator	Investigator-assessed date
3 cases: Millennium agreed with neither	Millennium's assessed date

[Source: The Applicant's response to our information request #4 dated August 13, 2015]

The Applicant claimed that sensitivity analysis results (Table 11), incorporating discordance between IRC and investigator assessments, were consistent with the primary analysis of the 1st interim PFS per IRC.

TABLE 11: SENSITIVITY ANALYSIS RESULTS OF 1ST INTERIM PFS ADDRESSING DISCORDANCE, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Events (%)	129 (35.8)	157 (43.4)
Progressed	114 (31.7)	145 (40.1)
Died	15 (4.2)	12 (3.3)
Median PFS (months) (95% CI)	20.6 (17.0, NE)	14.9 (13.0, 17.6)
Stratified Hazard Ratio (95% CI)	0.74 (0.59, 0.94)	
Nominal P value	0.012	

[Source: Ad hoc Table 2 in the Applicant's response to our information request dated August 13, 2015]

Updated final analysis results of PFS per investigator are listed in Table 12.

TABLE 12: FINAL ANALYSIS RESULTS OF PFS PER INVESTIGATOR, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Events (%)	175 (48.1)	189 (51.9)
Progressed	156 (42.9)	171 (47.0)
Died	19 (5.2)	18 (4.9)
Median PFS (months) (95% CI)	19.7 (17.7, 26.9)	17.7 (15.4, 21.2)
Stratified Hazard Ratio (95% CI)	0.86 (0.70, 1.06)	
Nominal P value	0.16	

- PFS: progression-free survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Table 1.d in the applicant's RFI response dated October 9, 2015 and Statistical reviewer's analysis]

Reviewer's note: For updated final analysis of PFS, the observed difference in median PFS per investigator between Ixazomib arm and placebo arm was 2 months compared to 4.1 months for PFS per IRC, the HR was 0.86 (95% CI: [0.70, 1.06]) , and the nominal p value was 0.16.

3.2.4.4 Discrepancy in the 1st Interim and Final PFS data

The data for the identified 19 patients from 1st IA underwent re-reading as part of final analysis. As a result of the re-reading, the date of PD changed for 13 patients, the censoring date changed for 3 patients, a censoring status changed to PD for 2 patients, and PD status changed to censoring in 1 patient. To evaluate the impact of the revised assessments in the 19 patients, the Applicant performed a sensitivity analysis incorporating the changes in observed PFS (Table 13). For instance, patients with newly confirmed PD after 30 October 2014 (the 1st IA DCO date) were censored at the 1st IA DCO in the sensitivity analysis, whereas for patients with newly confirmed PD before 30 October 2014, the new PD dates were used in the analysis.

TABLE 13: SENSITIVITY ANALYSIS RESULTS OF 1ST INTERIM PFS PER IRC ADDRESSING DATA ISSUES, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Events (%)	123 (47.6)	153 (52.4)
Median PFS (months) (95% CI)	NE (17.5, NE)	15.6 (13.0, 17.7)
Stratified Hazard Ratio (95% CI)	0.75 (0.59, 0.95)	
Nominal P value	0.015	

- PFS: progression-free survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Table 1.c in the Applicant's RFI response dated October 26, 2015]

Reviewer's note: The Applicant claimed that the sensitivity analysis, incorporating the changes in observed PFS due to data issues, confirmed the results of first interim analysis of PFS per IRC.

3.2.4.5 Other Sensitivity Analysis of PFS

Table 14 summarizes the analysis results for the 3 sensitivity analyses defined in Section 3.2.2. Sensitivity analysis results were consistent with those from the primary analysis of 1st interim PFS per IRC.

TABLE 14: FURTHER SENSITIVITY ANALYSIS RESULTS OF 1ST INTERIM PFS PER IRC, ITT POPULATION

	Median PFS (Months)		HR and 95% CI	Nominal P Value
	Ixazomib + LenDex	Placebo + LenDex		
Sensitivity analysis 1	20.6	14.7	0.74 (0.59, 0.94)	0.013
Sensitivity analysis 2	20.6	14.1	0.75 (0.59, 0.94)	0.014
Sensitivity analysis 3	20.6	14.1	0.73 (0.58, 0.92)	0.007

- HR: Hazard ratio; CI: confidence interval;

[Source: Statistical reviewer's analysis]

3.2.4.6 Secondary Endpoints Analysis Results

3.2.4.6.1 Analyses Results of 1st Interim OS

The first interim analysis results of OS based on 107 deaths are summarized in Table 15 and Figure 3. The hazard ratio for Ixazomib versus Placebo was 0.9 (95% CI: [0.62, 1.32]) with estimated median OS not achieved yet at the data cut-off time for both treatment arms.

TABLE 15: FIRST INTERIM ANALYSIS RESULTS OF OS, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Deaths (%)	51 (14.2)	56 (15.5)
Median OS (months) (95% CI)	NE	NE
Stratified Hazard Ratio (95% CI)	0.9 (0.62, 1.32)	
P value	0.59	

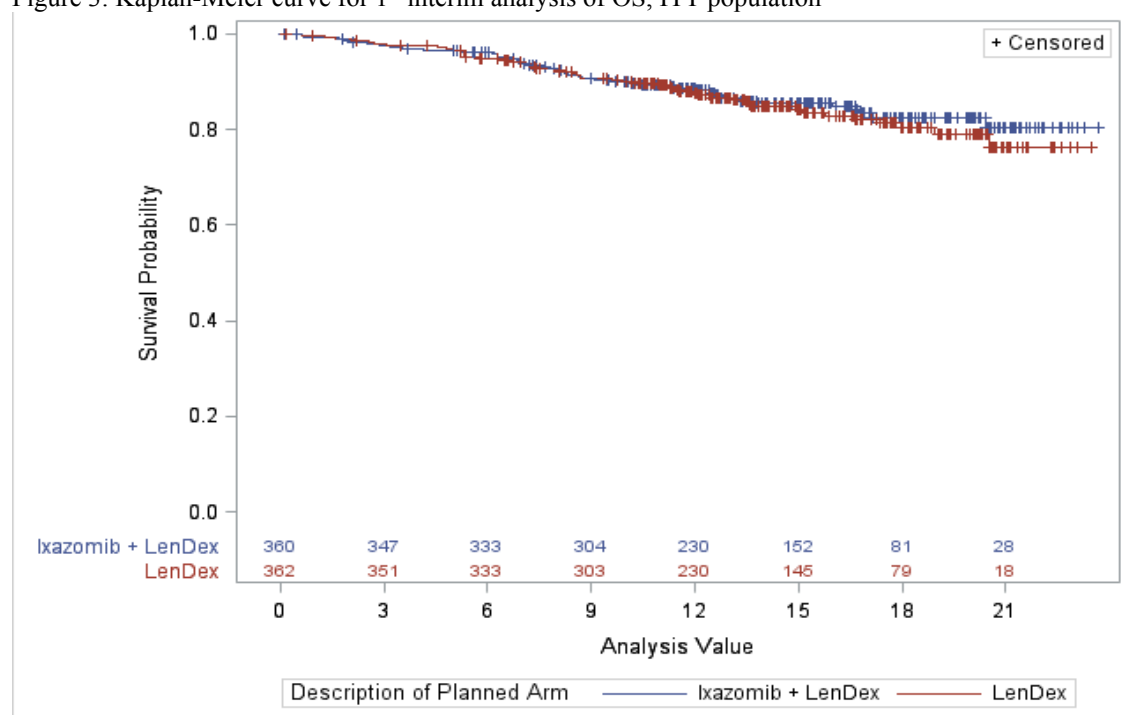
- OS: overall survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Statistical reviewer's analysis]

Figure 3: Kaplan-Meier curve for 1st interim analysis of OS, ITT population



[Source: Statistical reviewer's analysis.]

3.2.4.6.2 Analyses Results of 2nd Interim OS

There were 171 deaths in the 2nd interim analysis of OS, the median OS was still not achieved for either treatment arm (Table 16). The estimated HR was 0.87 and the p value was 0.36. The 2nd interim analysis results of OS were still not statistically significant.

TABLE 16: SECOND INTERIM ANALYSIS RESULTS OF OS, ITT POPULATION

	Ixazomib + LenDex (N=360)	Placebo + LenDex (N=362)
Deaths (%)	81 (22.5)	90 (24.9)
Median OS (months) (95% CI)	NE	NE
Stratified Hazard Ratio (95% CI)	0.87 (0.64, 1.18)	
Nominal P value	0.36	

- OS: overall survival; CI: confidence interval; NE: not evaluable/achieved;

- P value from a stratified log-rank test.

- Hazard ratio is from stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Table 1.a in the applicant's RFI response dated October 9, 2015 and Statistical reviewer's analysis]

3.2.4.6.3 Analysis Results of OS in High-risk Patients Harboring del(17)

A total of 69 patients (36 in Ixazomib arm and 33 in the placebo arm) had del(17) chromosomal abnormality in the myeloma plasma cells, which is a negative prognostic factor in MM. The results of OS in high-risk patients harboring del(17) are summarized in Table 17.

TABLE 17: ANALYSIS RESULTS OF OS IN HIGH-RISK PATIENTS HARBORING DEL17

	Ixazomib + LenDex (N=36)	Placebo + LenDex (N=33)
Deaths (%)	4 (11.1)	9 (27.3)
Median OS (months) (95% CI)	NE	NE
Un-stratified Hazard Ratio (95% CI)	0.39 (0.12, 1.25)	

- OS: overall survival; CI: confidence interval; NE: not evaluable/achieved;

- Hazard ratio is from un-stratified proportional hazard model. Hazard ratio < 1 favors Ixazomib arm.

[Source: Statistical reviewer's analysis]

Reviewer's note: Due to small sample size and number of events, HR was derived based on un-stratified Cox regression model, and this may not be a reliable estimate.

3.2.4.6.4 Analysis Results of Overall Response Rate (ORR)

Rates of overall response based on IRC assessment are summarized in Table 18.

TABLE 18: ANALYSIS RESULTS OF ORR PER IRC, ITT POPULATION

	Ixazomib + LenDex (N=360) n (%)	Placebo + LenDex (N=362) n (%)
Overall response rate (CR, PR), n (%)	283 (78.3)	259 (71.5)
CR	42 (11.7)	24 (6.6)
PR	240 (66.7)	235 (64.9)

[Source: Study C16010 CSR Page 143 Table 11.d]

Reviewer's note: While the 1st interim analysis of PFS per IRC was statistically significant, the observed difference was moderate, and there were no significant difference in observed OS and ORR results between two treatment arms so far.

3.2.4.7 Conclusions for Efficacy

The pivotal study C16010 demonstrated superiority in 1st interim analysis of PFS per IRC for Ixazomib in combination with lenalidomide and dexamethasone compared to Placebo in combination with lenalidomide and dexamethasone for subjects with relapsed or refractory multiple myeloma. The data for key secondary endpoint OS were not mature yet.

We identified some statistical issues in this submission:

- Although 1st interim analysis results of PFS per IRC crossed the pre-specified superiority boundary, the final analysis results of PFS were not statistically significant (Section 3.2.4.2).
- There were discordance between PFS per IRC and PFS per investigator. Analysis results for PFS per investigator were not significant for both the 1st interim and final analyses (Section 3.2.4.3).
- There were some discrepancies between 1st interim and final PFS per IRC data (Section 3.2.4.4).

Due to these issues, reliable estimate of the magnitude of treatment effect based on PFS could not be ascertained.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.4 Benefit-risk Assessment

This NDA application provided some evidence for the benefit of Ixazomib plus lenalidomide and dexamethasone over placebo plus lenalidomide and dexametasone for the treatment of patients with (b) (4) multiple myeloma, based on the 1st interim analysis results for PFS per IRC. However, due to some statistical issues identified in this submission, the observed PFS effect was not robust, and a reliable estimate of the magnitude of treatment effect on PFS could not be ascertained. Whether the submission demonstrated an overall favorable risk-benefit profile on Ixazomib is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Region

Table 19 summarizes the subgroup analyses of 1st interim PFS per IRC by gender, age, race and region for the study C16010.

Table 19: First Interim PFS per IRC – subgroup analyses by gender, age, race and region

Subgroup	Ixazomib + LenDex		Placebo + LenDex		HR* (95% CI)
	Event/N	Median (mos)	Event/N	Median (mos)	
Gender					
Male	74/207	21.4	86/202	14.7	0.75 (0.55, 1.03)
Female	55/153	18.4	71/160	14.1	0.73 (0.51, 1.06)
Age					
< 65 yrs	55/148	20.6	70/157	14.7	0.77 (0.53, 1.11)
≥ 65 yrs	74/212	18.7	87/205	14.1	0.76 (0.55, 1.04)
Race					
White	117/310	20.6	137/301	14.1	0.75 (0.59, 0.96)
Non-White	12/50	NE	20/61	15.6	0.87 (0.41, 1.85)
Region					
North America	15/47	NE	18/49	17.7	1.11* (0.56, 2.21)
Europe	95/247	20.6	113/236	13.2	0.70 (0.53, 0.92)
APAC	19/66	NE	26/77	NE	0.71* (0.39, 1.29)

*: Un-stratified HR.

HR: hazard ratio; CI: confidence interval; NE: not evaluable/achieved; APAC: Asia-Pacific.

[Source: Study C16010 CSR Page 174 Table 11.i and statistical reviewer's analysis.]

Reviewer's comment:

- Most patients were White in the Study C16010, therefore patients with race other than White were combined together as a subgroup of “Non-White”.
- Except for region of North America, no outliers were observed in subgroup analyses.

5 SUMMARY AND CONCLUSIONS

Ixazomib demonstrated its superiority in PFS per IRC over Placebo in the first interim analysis in the Study C16010. In Sections 5.1 and 5.2, we further discuss some statistical issues we have for this submission.

5.1 Statistical Issues

Here are the statistical issues we identified in this submission:

1. Final analysis results of PFS are not statistically significant.
2. Discordance between PFS per IRC and PFS per investigator.
3. Discrepancy in 1st interim and final PFS data
4. Much smaller treatment effect in subgroup of patients who received one prior therapy

5.2 Collective Evidence

Please refer to Sections 3.2.4.2 – 3.2.4.4 for further details for addressing issues 1 – 3 identified in Section 5.1. In this section, we presented the exploratory analyses to address the 4th issue we identified above.

5.2.1.1 Exploratory Subgroup Analyses

PFS curves as shown in Figures 1 and 2 overlap between two treatment arms for up to the first 9 months. We performed some exploratory subgroup analysis to explore the possible causes of this overlap. We found that although primary analysis of PFS per IRC was significant, the treatment effect of Ixazomib was much smaller for subjects received one prior therapy. Tables 20 summarize corresponding subgroup analysis results for 1st interim and final PFS per IRC by prior therapy.

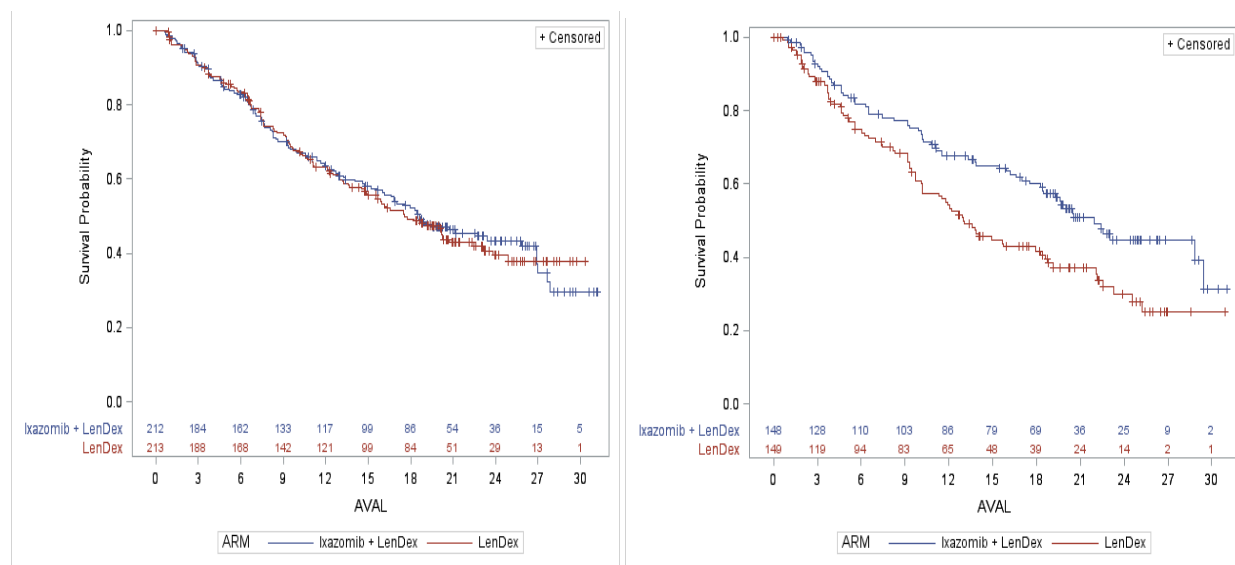
Table 20: First Interim and Final Analysis Results of PFS per IRC by Prior Therapy

Prior therapy (1 vs. 2 or 3)	Ixazomib + LenDex		Placebo + LenDex		Difference in medians	HR* (95% CI)
	Event/N	Median (mos)	Event/N	Median (mos)		
First interim analysis of PFS per IRC						
1	80/212	20.6	88/213	16.6	4.0	0.88 (0.65, 1.20)
2 or 3	49/148	NE	69/149	12.9	NE	0.58 (0.40, 0.84)
Final analysis of PFS per IRC						
1	109/212	18.7	112/213	17.6	1.1	0.99 (0.76, 1.29)
2 or 3	68/148	22.0	83/149	13.0	9.0	0.62 (0.45, 0.86)

HR: hazard ratio; CI: confidence interval; NE: not evaluable/achieved.

[Source: Statistical reviewer's analysis.]

Figure 4: Kaplan-Meier curve for final analysis of PFS per IRC by prior therapy 1 vs. 2 or 3



Reviewer's note:

- Prior therapy was one of the randomization stratification factors. Patient's demographics and baseline disease characteristics were balanced between two treatment arms for both subgroups: 1 prior therapy and 2 or 3 prior therapies.
- Figure 4 shows the K-M curves for the final PFS per IRC for patients with 1 prior therapy overlaps between two treatment arms, while the PFS curves for patients with 2 or 3 prior therapies separate from the beginning of the treatment.
- It suggests that the treatment effect observed in the overall population may be driven by the significant treatment effect in a subgroup, while the patients in the other subgroup may not benefit from the addition of Ixazomib to the backbone therapy of lenalidomide and dexamethasone. This hypothesis needs to be further evaluated prospectively.

5.3 Conclusions and Recommendations

This NDA application was based on a multicenter, Phase III, double-blind, randomized trial (C16010) comparing Ixazomib plus lenalidomide and dexamethasone versus Placebo plus lenalidomide and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma. The trial demonstrated statistically significant improvement in PFS for Ixazomib over placebo for treatment of patients with RRMM based on the 1st interim analysis of PFS per IRC. However, the final analysis results of PFS per IRC were not statistically significant. In addition, results for PFS per investigator were not significant for both interim and final analyses. Due to these issues, reliable estimate of the magnitude of treatment effect based on PFS could not be ascertained. The data for the secondary efficacy endpoint OS were not mature yet.

5.4 Labeling

We have the following recommendation for Ixazomib labeling:

- Because the updated final analysis results of PFS are available now, we recommend the updated final instead of 1st interim analysis results of PFS should be included in the labeling to provide a more accurate description of the treatment effect.
- The Applicant included a p value of 0.01 for 1st interim PFS analysis in the labeling. We recommend if 1st interim analysis results will be used in the labeling, p value < 0.05 be listed because p value from updated final PFS analysis was 0.0548.
- We disagree with the proposed (b) (4)
Because the first key secondary endpoint overall survival was not statistically significant, (b) (4)

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/s/

YUN WANG
10/30/2015

LEI NIE
10/30/2015

RAJESHWARI SRIDHARA
10/31/2015